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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/020,241	12/18/2001	Uwe Heinelt	02481.1763-00	8753

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EXAMINER
RAO, DEEPAK R

ART UNIT	PAPER NUMBER
1624	7

DATE MAILED: 07/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/020,241	Heinelt et al.
Examiner	**Art Unit**
Deepak Rao	1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 22, 2003*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *1 & 4*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 1-34 are pending in this application.

Election/Restriction

Upon reconsideration, the restriction requirement of the previous office action is hereby withdrawn and all pending claims have been examined together.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of most of the disorders of the claims such as ischemia, does not reasonably provide enablement for the treatment or prophylaxis of all other disorders of the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the

art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The instant claims are drawn to "a method for the treatment or prophylaxis" of assorted types of disorders including those of respiratory drive, snoring, kidney disorders, cell proliferation, etc. The use disclosed in the specification is as NHE3 inhibitors, useful to treat a laundry list of diseases, which include respiratory disorders, kidney disorders, cell proliferation, etc. Test assays and procedures are provided in the specification in Example 32 related to NHE and the inhibitory activity data for some of the compounds of the invention is provided in Table 3, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the diverse disorders of the instant claims. The disorders encompassed by the instant claims include cell proliferative disorders, ischemic conditions of the CNS system, respiratory disorders, etc., some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, see MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, as evidenced by the wide range of results obtained for the tested compounds. It is inconceivable as to how the claimed compounds can treat the laundry list of

diseases embraced by the claims having diverse mechanisms. A state of the art reference (see Gekle et al.) in the filed of NHE3 receptor activity, states that "More work is required in order to determine the precise role of NHE3 in the regulation of receptor mediated endocytosis and to investigate the mechanisms underlying the establishment of the Na+ gradient across the endosomal membrane", see page 719, col. 2. Also, Cavet et al. (Am. J. Phys. Cell Phys. 2001) express that "Although both are located on the apical surface of renal and intestinal epithelial cells, in many species their relative roles have not yet been fully defined". Thus, the predictability of the activity of the NHE3 type inhibitors is considerably low as can be seen from the state of the art.

For example, instant claim 17 is drawn to the 'treatment of a cell proliferative disorder', which is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the

enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Many of the claims recite "**prophylaxis**" of the above diseases. Therefore, the scope of the claims includes not only treatment but also "**prevention** of a disease" which is not adequately enabled solely based on the kinase inhibitory activity of the compounds provided in the specification. "To prevent" actually means *to anticipate* or *counter in advance, to keep from happening etc.* (as per Websters II Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no evidence of record which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein. Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999) wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'preventive' effect solely based on the inhibitory activity disclosed for the compounds.

Further, the instant claims recite "treatment of a state of shock", "method for use in surgical operation", "treatment or prophylaxis of attack by an ectoparasite" which have not been explained fully in the specification and there is no enablement for these claims.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. The term "derivative" in the preamble of the claim is not proper Markush language. The term 'derivative' is open ended. This term would allow for groups other than those

recited in the claim. Replacing the above recitation with -- compound -- (**in all occurrences**) is suggested.

2. Claim 7 recites formula (III) wherein there is no definition provided for the variables A' and A".

3. Claim 28 recites "a method for use in surgical operation or an organ transplantation ...", it is not clear what is intended by this claim. The specification does not provide any help.

4. Claim 29 recites "a method for the conservation or storage of a transplant for surgical measures" it is not clear what is intended by this claim. The specification does not provide any help.

5. Claim 32 recites "a method for the treatment or prophylaxis of attack by an ectoparasite" it is not clear what is intended by this claim. The specification does not provide any help.

Claims not particularly addressed above are included here because they are dependent claims and do not further resolve the above issues.

Allowable Subject Matter

Claims 1-16 and 33-34 would be allowable if rewritten or amended to overcome the rejection(s) under 35 U.S.C. 112, second paragraph, set forth in this Office action. The references of record do not teach or fairly suggest the instantly claimed compounds. The closest reference of record, Ricks et al., U.S. Patent No. 6,355,660 teaches structurally similar compounds, see for example, compound 206 in col. 85-86, however, the reference compounds

have a carbonyl group (C=O) separating the nitrogen and the Het group as compared to the instant claims wherein A is a C_1-C_4 alkylene, e.g., -CH_2-.

Receipt is acknowledged of the Information Disclosure Statements filed on December 18, 2001 and November 16, 2002 and copies are enclosed herewith.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (703) 305-1879. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (703) 308-4716. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Deepak Rao
Primary Examiner
Art Unit 1624

July 9, 2003